UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:	:	
	:	
MIRENA IUS LEVONORGESTREL-RELATED PRODUCTS LIABILITY LITIGATION (NO. II)	:	**17-MD-2767 (PAE)** **17-MC-2767 (PAE)**
	:	
This Document Relates to All Actions	:	
	:	

DEFENDANTS' OPPOSITION TO PLAINTIFFS' OMNIBUS MOTION TO EXCLUDE GENERAL CAUSATION EXPERT TESTIMONY OF DEFENDANTS' EXPERT WITNESSES

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases **Page(s)**

Other Authorities

PRELIMINARY STATEMENT

Plaintiffs' motion misrepresents the opinions and methodologies of Bayer's experts, relies on lawyer-driven arguments not sponsored by any of the Plaintiffs' experts, and wrongly seeks to impose a burden on defense experts to do more than demonstrate the flaws in the plaintiff experts' theories of causation. After their rhetoric is cleared away, Plaintiffs are left with no basis to exclude Bayer's well-qualified experts, all of whom offer reliable and methodologically-sound opinions about the fundamental flaws in every element of the plaintiff experts' theories.

LEGAL STANDARD

Bayer incorporates by reference the discussion of the *Daubert* standard in its Omnibus Memorandum in Support of Motions to Exclude the Plaintiff Experts.[1]

ARGUMENT

I. Plaintiffs Improperly Attempt to Shift the Burden to Bayer to Prove More Than the Fact That Plaintiffs' Theories Are Flawed.

In this medical product liability litigation, like any other, Plaintiffs bear the burden of demonstrating a causal relationship between the medication at issue (Mirena) and the negative outcome alleged (IIH); this burden must be met by proffering reliable expert testimony that

[1] One point bears mentioning in response to Plaintiffs' characterization of *Daubert*, which appears to be geared as much toward protecting Plaintiffs' own experts as anything else. Plaintiffs offer no factual or legal support for their blanket statement that the *Daubert* reliability factors should not apply to "pathophysiological" opinions, such as hypothetical biological mechanisms, supposedly because such opinions "are not easily evaluated by testing or error rates." Pl. Omnibus Br. at 2-4. Indeed, their own mechanism expert, Dr. Johanson, testified that "a week's research could answer some pivotal questions," even though he did no such research. Ex. 6, Johanson Dep. 15:1-2, 17:5-18:6. Even if Plaintiffs could identify a specific problem that prevented a specific "pathophysiological" opinion from being tested, the Court could consider it on a case-by-case basis without having to exclude all "pathophysiological" opinions from scrutiny under the *Daubert* reliability factors. *See Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 593 (1993) (reliability factors are not a "definitive checklist or test").

satisfies Federal Rule of Evidence 702 and *Daubert*. *See In re Mirena IUD Prod. Liab. Litig.*, 202 F. Supp. 3d 304, 310-311 (S.D.N.Y. 2016), *aff'd*, 2017 WL 4785947 (2d Cir. Oct. 24, 2017).

In response to the opinions offered by Plaintiffs' experts, Bayer's experts explain that there is no reliable evidence that Mirena can cause IIH. *In re Mirena IUD Prod. Liab. Litig.*, 169 F. Supp. 3d 396, 418 (S.D.N.Y. 2016), *aff'd*, 2017 WL 4785947 (2d Cir. Oct. 24, 2017). In these circumstances, "pointing to the absence of convincing studies or the weaknesses of studies on which Plaintiffs rely, and evaluating them in light of [Bayer's experts'] clinical experience, training and research, is . . . a logical and valid approach." *Id.* at 418-19. Yet Plaintiffs seek to impose an artificial, burden-shifting standard on Bayer's experts, essentially suggesting that Bayer's experts must fill the gaps that Plaintiffs' own experts cannot.

Explaining what causes IIH: Plaintiffs press the specious argument that Bayer's experts should not be allowed to opine on Mirena and IIH unless they can explain what causes IIH — a condition whose cause and mechanism are unknown, by consensus of the scientific community. Def. Omnibus Br. at 2 & n.1; *see also, e.g.*, Pl. Newman Br. at 2 ("Dr. Newman says that the cause of IIH is unknown. Therefore, she precludes herself from offering any admissible opinion on the subject of Mirena's causal relationship with IIH."); Pl. Gossett Br. at 6 (criticizing Dr. Gossett for a "lack of background knowledge regarding [IIH]" because she testified that "[w]e just don't know what [the cause] is at this time"). But "[d]efendants . . . do not bear the burden of proving causation." *See In re Ethicon, Inc. Pelvic Repair Sys. Prod. Liab. Litig.*, 2017 WL 6396852, at *2 (S.D. W.Va. Dec. 13, 2017).

Conducting original research studies: Elsewhere, Plaintiffs suggest that Bayer's experts should be excluded for failure to conduct independent studies investigating Mirena and IIH. *See, e.g.*, Pl. Van Stavern Br. at 2 ("Dr. Van Stavern did not conduct his own studies to support his

opinion."); *id.* at 3 ("Dr. Van Stavern has conducted zero epidemiological studies"). But "[e]xperts need not conduct studies of their own in order to opine on a topic; a review of other studies and scientific literature can be enough to qualify experts to testify and to make that proposed testimony reliable." *Mirena*, 169 F. Supp. 3d at 412.

Precisely quantifying every criticism of Plaintiff experts' theories: Plaintiffs also repeatedly claim, again without legal support, that Bayer's experts must precisely quantify their criticisms of Plaintiffs' hypothesized relationship between Mirena and IIH, and that to criticize the central article relied upon by Plaintiffs' experts — Valenzuela — Bayer's experts must go further, and correct each of Valenzuela's errors.

For example, Plaintiffs object to the concept of "preferential prescribing" — that is, to the fact that obese women are preferentially prescribed Mirena over other contraceptives, consistent with widely-accepted medical recommendations,[2] and that Mirena users are more likely to be obese than the general population of reproductive-age women — and argue that Bayer's experts should be excluded because they have not precisely quantified how many Mirena users are obese. Pl. Omnibus Br. at 16-17. Yet Valenzuela itself acknowledges that preferential prescribing exists, with this confounding implicating that study's ultimate analysis. Ex. 64, Valenzuela 2017 at 5 ("[IIH]is more likely to occur in the same population of women who are more likely to have [Mirena] recommended to them by their physician," including "women with obesity"); *id.* ("Although use of [Mirena] seems be associated with an increased risk of [IIH], *it is possible that this observation occurred because use of [Mirena] is also associated with other established risk factors that are known to be associated with [IIH] (e.g., obesity and recent*

[2] *See, e.g.*, Ex. A (attached hereto), ACOG 2006 at 1462; Ex. 43, Marnach 2013 at 297-98; Ex. 77, Med. Eligibility Criteria 2016.

weight gain)") (emphasis added).[3]

Plaintiffs' criticisms — that Bayer's experts do not "quantify" the degree of preferential prescribing — fundamentally misstate the role of a defense expert. "When offering expert testimony, the defendant has 'no burden to produce models or methods of their own; they need only attack those of the plaintiffs' experts.'" *Scott v. Chipotle Mex. Grill*, 315 F.R.D. 33, 44 (S.D.N.Y. 2016). Bayer's experts' burden is simply to show that Plaintiffs' theories are flawed. *See Mirena*, 169 F. Supp. 3d at 418. Bayer's experts have done this and more: they provide five studies validating preferential prescribing in practice in clinical settings (Peipert 2011, Scott-Ram 2012, Saito-Tom 2015, Bhuva 2017, Mosher 2017); they demonstrate that preferential prescribing has not been taken into account in Valenzuela; and they show that Valenzuela itself admits to this limitation. Even Plaintiffs' own experts concede that if Valenzuela had controlled for obesity — in other words, accounted for preferential prescribing— the study's odds ratio would decrease. Ex. 8, Moyé Dep. at 220:21-25 (he would "expect [the risk] to decrease had Valenzuela controlled for weight[.]"); Ex. 14, Wheeler Dep. at 193:14-194:7 (failing to control for obesity could affect both the outcome and the exposure).

II. Bayer's Experts' Straightforward Reanalysis of the Valenzuela Study Was Appropriate and Methodologically Sound.

Plaintiffs' experts cite the Valenzuela study as support for their opinions, and thus Bayer's experts critically evaluate Valenzuela to assess its reliability and whether it supports a causal relationship between Mirena and IIH. While Plaintiffs grouse that Bayer's experts present more detailed critiques of the Valenzuela study than of other studies, *see, e.g.*, Pl. Omnibus Br. at 7, 10, 18-20, the fact is that Valenzuela warrants greater scrutiny because it is an outlier as the

[3] Except where noted otherwise, the exhibits referenced herein are contained in Defendants' compendium of exhibits (Dkt. 167).

only epidemiologic study purporting to find a statistically significant association between IIH and Mirena, or IIH and levonorgestrel more broadly.

Bayer's experts appropriately identify Valenzuela's numerous methodological flaws and limitations — many of which the Valenzuela authors specifically acknowledge — and conclude that the paper cannot support an association between Mirena and IIH, much less a causal relationship. Bayer's experts are not obligated to correct Valenzuela's many errors (and indeed they cannot correct errors such as the failure to control for obesity or age, because the Valenzuela authors did not collect the necessary data). It is enough that they identify these errors to demonstrate that the study's statistical findings cannot be accepted at face value, as Plaintiffs' experts have done. *See Chipotle*, 315 F.R.D. at 44.

Yet some of Bayer's experts go one step beyond and illustrate the profound effect of correcting for *just one* of Valenzuela's self-acknowledged errors: "underestimat[ing] the number of women with an LNG-IUS[.]" Ex. 64, Valenzuela at 5. By *underestimating* the rate of Mirena use in both sets of study controls (Utah and Danish arms), Valenzuela systematically *over-estimated* the relative rate of Mirena use between the IIH (case) groups and the non-IIH (control) groups — that is, it concluded that women with IIH were significantly more likely to use Mirena than women without IIH.

Unable to argue that Valenzuela *did* appropriately estimate Mirena use in its control groups — after all, both Valenzuela and Plaintiffs' own experts have conceded this point[4] — Plaintiffs make the novel and entirely unsupported argument that Bayer's experts should be excluded for providing an example of how correcting for Mirena use in Valenzuela's Denmark

[4] Ex. 8, Moyé Dep. at 169:2-21, 196:18-197:10, 200:1-10; Ex. 2, Darney Dep. at 183:1-9, 186:15-187:3.

and Utah control arms would materially affect the study's results.

A. The Denmark Arm

When estimating Mirena use in Danish controls, the Valenzuela authors did not examine the controls' medical records, as they did for the IIH patients (cases). Instead, the authors determined the number of Mirenas sold in Denmark in a single year, divided that by the number of women of reproductive age in Denmark, and — finding that enough Mirenas were sold in a year that 3.5% of Danish women of reproductive age could receive a Mirena in the year — estimated that a total of 3.5% of Danish women used Mirena. As Bayer's experts explained, the 3.5% estimate does not account for the fact that the product is normally used for multiple years at a time. *See, e.g.*, Pl. Barnhart Ex. A, Rpt. 48 ("That assumption is clearly in error, because it treats Mirena as if it is used only for one year. . . "). In any given year, current users include women who began Mirena in the given year and women who have continued using Mirena from prior years. Mirena is approved for up to five years of use, and while not all women use it for the full five years, studies have shown that average use is well beyond one year. Pl. Barnhart Ex. A, Rpt. at 48, citing Ex. B (attached hereto), Diedrich 2015; *see also* Ex. 49, Peipert 2011 at 1111 & tbl. 4 (87.5% continuation after one year).

Understanding that single-year sales figures do not accurately estimate total usage of a multi-year-use product at any given time, Bayer's experts analyzed the peer-reviewed literature to estimate Mirena use in Denmark. In addition to using Diedrich 2015 (which permits a reasonable finding of at least 10% total use, with an average use of at least 3 years), Bayer's experts also cited Lindh 2017, which drew its figures from Danish government data, and Cibula 2008. Pl. Omnibus Br. at 20; Ex. 42, Lindh 2017; Ex. 20, Cibula 2008 at tbl. 2 (June 2006 survey finding 9% Mirena use in Scandinavian women).

Plaintiffs misconstrue Lindh. First, they claim that the study only shows "*relative*" use of

Mirena, Pl. Omnibus Br. at 20, despite the fact that Lindh expressly shows relative use *and* absolute use of Mirena, Ex. 42, Lindh 2017, at 23 fig. 1 (showing absolute use in the top chart, and relative use in the bottom chart), and despite the concession of their own expert epidemiologist, Dr. Moyé, that he had seen no data consistent with Valenzuela's estimated 3.5% use in Denmark. Ex. 8, Moyé Dep. at 196:18-197:10, 200:1-10. Contrary to the argument that Bayer's experts claim there were "nearly three times as many Mirena prescriptions in 2013 as there were sales in 2014," Pl. Omnibus Br. at 20, Bayer's experts simply account for the fact that a Mirena "prescription" has a useful life of greater than one year.

Second, Plaintiffs also claim that the Lindh figures were generated by "arbitrarily" setting the mean duration of LNG-IUS use at four years, *id.* at 20, but the estimate of four years is well supported by published literature. *See* Ex. B (attached hereto), Diedrich 2015 at 1.e1-e2. Estimating 10% Mirena use in controls, rather than Valenzuela's estimate of 3.5%, yielded a finding of no statistically significant difference in Mirena use between case and controls. Even more conservative estimates, such as 8% use, yielded the same result. *See, e.g.*, Pl. Langer Ex. A, Rpt. at 30-33; Pl. Lee Ex. A, Rpt. at 37-42; Pl. Dalton Ex. D, Rpt. at 22-25.

B. The Utah Arm

As with the Denmark arm of their study, the Valenzuela authors underestimated Mirena use among controls in the Utah arm of the study. Ex. 64, Valenzuela at 5. Although the authors examined billing records for Mirena insertions at the University of Utah hospital system during the 2008-2013 study period, their method of estimating use has at least two significant data gaps: (1) patients in the hospital system could have received Mirena at another facility (for example, a local private ob-gyn or free clinic), but they would not have been counted as "users" under the study design; and (2) patients in the hospital system who started using Mirena before 2008 and continued using it into the study period would not have been counted as "users." Plaintiffs'

epidemiologist Dr. Moyé agreed both that under-counting Mirena use was a "valid concern," and that he had never seen estimated Mirena use rates consistent with Valenzuela's low estimate (approximately 2% of controls had billing records for Mirena insertions during the 2008-2013 study). Ex. 8, Moyé Dep. at 169:2-21, 196:18-197:10, 200:1-10. Likewise, Plaintiffs' expert Dr. Darney agreed that Valenzuela may have "underestimated the use of Mirena in the control group in both studies[.]" Ex. 2, Darney Dep. at 186:15-187:3.

Recognizing these errors, Bayer's experts turned to the peer-reviewed medical literature for a reasonable, reliable, and conservative estimate of Mirena use among Utah women. Contrary to Plaintiffs' claims, Bayer's experts did not "arbitrarily move[] 17,682 women from the non-Mirena control group to the Mirena control group[,]" Pl. Omnibus Br. at 18, when stating that a reasonable estimate supported approximately 7-10% Mirena use in the controls. Although Plaintiffs' lawyers seek to confuse the issue, Bayer's experts' estimates were based on a straightforward review of the literature. Plaintiffs did not provide Bayer's experts much opportunity to explain their logic during their depositions, but the following explanation tracks the points Dr. Barnhart was able to make at his deposition and that appear in the experts' reports. Ex. B, Barnhart Dep. 80:1-83:9; *see also, e.g.,* Pl. Barnhart Ex. A, Rpt. at 42-43; Pl. Lee Ex. A, Rpt. at 35-38; Pl. Langer Ex. A, Rpt. at 28-29.

- **Step 1:** CDC data reported in **Boulet 2016** shows that **18.9%** of women aged 18-44 in Utah who were at risk for unintended pregnancy used a long-acting reversible contraceptive (LARC). At 18.9%, Utah had the highest rate of LARC use for the 17 states reporting data. Ex. 19, Boulet 2016 at 781 & 782 tbl. 1.
- **Step 2:** Understanding that not all LARCs are Mirena, the experts attempted to estimate the percentage of Utah women using Mirena specifically. **Sanders 2016**

shows that in the University of Utah system (where the Valenzuela study was conducted), 75% of women using LARCs used Mirena. Ex. 59, Sanders 2016 at 590.e3. The relevant calculation: 75% of 18.9% is 14.2%. In other words, approximately **14.2%** of Utah women of reproductive age who are at risk for unintended pregnancy use Mirena.

- **Step 3:** Understanding that not all women of reproductive age are at risk of unintended pregnancy, the experts used the literature to estimate what percentage of women in the age range *are* at risk. The Boulet study explained that "[w]omen were considered at risk for unintended pregnancy if they were not currently pregnant, were sexually active (not abstinent), and, the last time they had sex, had not had a hysterectomy, did not have a same-sex partner, and did not want a pregnancy." Here, the experts turned to **Jones 2012** — another study of CDC data — to estimate the percentage of reproductive-aged women at risk for unintended pregnancy. Ex. C (attached hereto), Jones 2012. Jones Table 1 shows the following percentages of women aged 15-44 fell into categories considered "not at risk" by Boulet:

    - currently pregnant: 5.0% ("pregnant or postpartum")
    - abstinent: 21.1% (11.8% "never had intercourse" and 7.3% "no intercourse in 3 months before interview")
    - had a hysterectomy: 0.4% ("surgically sterile, female")
    - same-sex partner: *not included in Jones*
    - wanted a pregnancy: 4.0% "seeking pregnancy"
    - Total: **30.5% "not at risk"** – meaning that approximately **70%** of reproductive-aged women **are at risk** for unintended pregnancy.

    Jones supports the same finding when read in the alternative:

    - 62.2% using some form of contraception[5]

[5] Plaintiffs attempt to re-categorize the CDC data by arguing *ipse dixit* that the 16.5% of women using "female sterilization" for contraception are not at risk for unintended pregnancy. Plaintiffs cite no medical literature or expert testimony to support this point. Pl. Omnibus Br. at 19; Pl.

  - 7.7% had intercourse in 3 months before the interview, no contraception
  - Total: **69.9% at risk** for unintended pregnancy.

- **Step 4:** Finding that approximately 70% of reproductive-aged women are at risk for unintended pregnancy, the experts adjusted down their estimated 14.2% Mirena use. Multiplying 14.2% by 70% yields 9.94%, meaning that a reasonably conservative methodology estimates that approximately 10% of all women in Utah aged 18-44 were using Mirena.

- **Step 5:** Using the adjusted estimates for Mirena use in Valenzuela's controls, the experts calculated new odds ratios and confidence intervals. Using standard statistical packages, all found that 10% Mirena use among controls yielded a non-significant finding — that is, no significantly higher (or lower) rate of Mirena use in the IIH cases compared to the non-IIH controls. Several experts then conducted even more conservative estimates, using 7-8% Mirena use in controls. These estimates still showed non-significant results, meaning no statistically significant difference in Mirena use rates between the cases and controls.

While Plaintiffs attack Bayer's other experts for analyzing Valenzuela "the same way," Pl. Omnibus Br. at 18, this criticism is not a *Daubert* challenge but merely a disagreement with Bayer's experts' conclusions — which were based on peer-reviewed, published literature. A party "is not entitled to have [an expert's] opinion excluded merely because it disagrees with the conclusion that [the expert] reached." *Skyhook Wireless, Inc. v. Google, Inc.*, 2015 WL

Barnhart Br. at 11. Their position is demonstrably wrong. As Dr. Barnhart explained, "female sterilization" such as tubal ligation is a form of contraception with a known failure rate, and published data shows it to be less effective than Mirena. Pl. Barnhart Ex. B, Dep. at 91:7-12, 98:9-11; Pl. Barnhart Ex. A, Rpt. at 13 (citing a "0.2% failure rate for Mirena" and "0.5% per woman-year failure rate . . . [for] a tubal ligation").

13620764, at *4 (D. Mass. Feb. 18, 2015).

III. Bayer's Experts Have Addressed the Relevant Data.

A. Bayer's Experts Considered Everything That The Plaintiff Experts Considered and More.

In their omnibus motion and in their individual motions to exclude Bayer's experts, Plaintiffs argue that Bayer's experts failed to undertake a thorough review of the medical literature and other data before reaching their opinions. *See, e.g.,* Pl. Omnibus Br. at 12-14 (Norplant literature), 24-25 (proposed mechanism literature); Pl. Lee Br. at 1-2 ("*nothing* in Dr. Lee's report shows him doing *anything* other than reviewing Bayer's signal assessments and then performing the exact same analysis Bayer performed[;]" and Dr. Lee "*admits he reviewed virtually nothing*.") (emphasis added). Plaintiffs' claim is, quite simply, false. Not only did Bayer's experts review and rigorously analyze all the data and literature cited by Plaintiffs' experts to support their claims, but they evaluated materials that were not considered by most or all of Plaintiffs' experts, such as literature exploring whether there is an association between oral contraceptive use and IIH, and the Etminan 2015 cohort analysis (the epidemiological comparison of Mirena patients to oral contraceptive patients).

Plaintiffs' sweeping and unsubstantiated claim that "Bayer's experts have simply refused to review the literature and data presented to them by Dr. Salpietro, Dr. Johanson, and Dr. Darney" regarding Plaintiffs' mechanism theories is also demonstrably false. Pl. Omnibus Br. at 24-25. Bayer's experts have addressed Plaintiffs' hypothesized biological mechanisms and have reviewed dozens of articles and abstracts cited by Plaintiffs' experts to support their mechanism theories. *See, e.g.*, Pl. Barnhart Ex. A, Rpt. at 78-82; Pl. Jusko Ex. A, Rpt. at 9-11; Pl. Newman Ex. K, Rpt. at 7, 13-15; Pl. Dinkin Ex. 4, Rpt. at 12-14; Pl. Rizzo Ex. B, Rpt. at 16-20; Pl. Van Stavern Ex. B, Rpt. at 12-14; Pl. Cestari Ex. A, Rpt. at 20-22.

B. Whether Bayer's Experts Considered the Empirica Database Is Irrelevant.

Plaintiffs fault Bayer's experts for not considering "Bayer's own internal disproportionality analyses" generated by Empirica, a software tool Bayer uses to help analyze adverse event data.[6] *See, e.g.*, Pl. Omnibus Br. at 23-24, Pl. Barnhart Br. at 15-17; Pl. Langer Br. at 19-20; Pl. Lee Br. at 7. Plaintiffs claim that because Bayer's experts did not review the Empirica-generated spreadsheets, their opinions on both disproportionality analyses (what Empirica calculates, albeit roughly and not tailored to Mirena)[7] and causation (which Empirica cannot evaluate) are inadmissible. Plaintiffs' argument is flawed in several key respects.

First, none of Plaintiffs' experts relied on Empirica data, so Bayer's experts had no burden to review the data in responding to the plaintiff experts' opinions. *See Chipotle*, 315

[6] The Empirica software automatically generates output containing certain comparisons of adverse event data. Ex. D (attached hereto), Manlik Dep. 70:23-71:24. An adverse event report is a report of an effect experienced by someone who has used a medication, regardless of whether there is any connection between the adverse event and medication. Pl. Barnhart Ex. A, Rpt. at 10.

[7] Disproportionality analysis is a procedure by which adverse event reports for one product can be compared to those for all other products in the same database in order to test whether the adverse event reports provide a "signal" of a potential association for a specific product-event combination. It provides a statistical method to assess whether a given adverse event is being reported by users of a given drug at a higher (or lower) proportion of all adverse events for that drug than the same adverse event is being reported by users of other drugs. Pl. Barnhart Ex. A, Rpt. at 11. Empirica runs automated monthly disproportionality analyses for more than 1.7 million product and event combinations. Ex. D (attached hereto), Manlik Dep. 84:9-85:17. The analysis is not tailored to Mirena-specific concerns, so that adverse event reports of IIH among Mirena users (who are exclusively women and nearly all of reproductive age) are compared to adverse event reports of IIH among *any* users of *any* other medications in the database. Ex. E (attached hereto), Empirica Signal Monthly Runs. Because Empirica runs a general query, rather than a query specifically tailored to Mirena, it would be expected to yield "disproportionate" reporting of IIH among Mirena users where a customized Mirena analysis may not, simply because Mirena users, as women of reproductive age, have an increased baseline risk of IIH compared to the general population. *See. e.g.,* Etminan 2017 (disproportionality analysis that did not use a comparison group limited to women of reproductive age yielded false positive association; appropriately controlling the analysis yielded no significant association between Mirena and IIH).

F.R.D. at 44.[8] Indeed, if this criticism of Bayer's experts were disqualifying, it would equally doom Plaintiffs' own experts.

Second, Empirica can only be used to generate a disproportionality analysis of adverse event reports, but a disproportionality analysis "is not a tool for establishing causal attributions between products and adverse events"; at most it can generate a signal for further evaluation. Ex. 78, 2005 FDA Guidance at 8; *see also* Pl. Barnhart Ex. A, Rpt. at 11; Pl. Lee Ex. A, Rpt. at 11-12; Pl. Langer Ex. A, Rpt. at 8. If the data cannot demonstrate causation, there can be no methodological failure in not considering it as part of a causation opinion. *See In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 807-08 (N.D. Ohio 2004) ("proportional reporting rate analyses are incomplete and often misleading," and "such evidence is insufficient to create a genuine issue of material fact regarding general causation"), *aff'd*, 447 F.3d 861 (6th Cir. 2006).

Third, the value of the Empirica data is further limited because the monthly signal detection process by design provides only a very rough analysis: it does not account for key variables such as gender, age, or obesity. Ex. E (attached hereto), Empirica Signal Monthly Runs. This limitation would have special implications for Mirena, which is used exclusively in women, almost all of whom are reproductive-aged and already at increased baseline risk for IIH, and thus disproportionate reporting of IIH in Mirena users in the Empirica data would be unsurprising but also meaningless. Relying on the simple output of the Empirica data would be to commit the same mistakes of Etminan et al. in their now-retracted disproportionality analysis — an analysis that both Plaintiffs' counsel and most of their experts thoroughly abandon.

When Plaintiffs' counsel confronted Bayer's experts with Plaintiffs' argument regarding

[8] Plaintiffs requested Empirica data late in the discovery process, and Bayer produced before Plaintiffs' expert reports were due. Ex. I (attached hereto), Shepherd Email.

the Empirica data, Plaintiffs either asked Bayer's experts about disproportionality analyses in the abstract, *see, e.g.*, Pl. Langer Ex. B, Dep. at 186:22-189:22, or they refused to provide the experts with the necessary data to evaluate how Empirica calculated its disproportionality analyses. For example, at Dr. Barnhart's deposition, Plaintiffs presented Dr. Barnhart with only part of the Empirica report and *withheld the portion he repeatedly requested*: an explanation of Empirica's comparison group. Pl. Barnhart Br. at 16-17 (*e.g.,* "they may have compared it to the entire database[,]" "I need to know who you're comparing it to[,]" and "it needs to be compared to people that would take Mirena. You can't compare it to children. You can't compare it to adult — to men. You can't compare it to women above age something. So the comparison is everything."). Despite Dr. Barnhart's repeated requests, Plaintiffs' counsel refused to provide the comparative group information. In the end, the withheld page confirmed precisely Dr. Barnhart's concern: the Mirena analysis included comparisons to men, children, and women beyond child-bearing age, Ex. E (attached hereto), Empirica Signal Monthly Runs, yielding a disproportionality estimate that reflects the population of Mirena users, but provides no information about Mirena use itself.

C. Bayer's Experts Sufficiently Applied the Bradford Hill Criteria.

Plaintiffs fault several of Bayer's experts for allegedly not "rigorously applying Bradford Hill." Pl. Omnibus Br. at 8. First, as Bayer's experts described, the Bradford Hill criteria only apply where "observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance." Ex. 35, Hill 1965 at 295; *see also* Pl. Langer Ex. A, Rpt. at 9; Pl. Barnhart Ex. A, Rpt. at 57; Pl. Hewitt Ex. A, Rpt. at 24; Pl. Van Stavern Ex. B, Rpt. at 15; Pl. Dinkin Ex. 4, Rpt. at 13; Pl. Lee Ex. A, Rpt. at 5; Pl. Dalton Ex. D, Rpt. at 27. As Bayer's experts methodically explained, no such "perfectly clear-cut" association had been established: only two published studies (Etminan and Valenzuela) have ever examined

Mirena and IIH, and neither provides clear-cut evidence of an association. *See id.*[9]

Second, Plaintiffs simply disregard the record when they claim that Bayer's experts "use[d] their *ipse dixit* rejection of Valenzuela 2017 as an excuse for not rigorously applying Bradford Hill." Pl. Omnibus at 8. Indeed, while the analysis called for by Bradford Hill would not be applicable in the absence of a clear-cut association, Bayer's epidemiology experts nevertheless engaged in lengthy and in-depth Bradford Hill analyses. For example, Dr. Barnhart and Dr. Lee each devoted more than a dozen pages of their reports to applying the Bradford Hill factors and responding to Dr. Moyé's misapplication of those factors. Pl. Barnhart Ex. A, Rpt. at 57-61, 67-77; Pl. Lee Ex. A, Rpt. at 4-8, 43-46, 48-53; *see also, e.g.*, Pl. Dalton Ex. D, Rpt. 27-32; Pl. Dinkin Ex. 4, Rpt. 13-14; Pl. Langer Ex. A, Rpt. 40-43, 45-50. Indeed, the meticulous discussions of the Bradford Hill criteria set forth by Bayer's experts in their reports demonstrate the unreliability of the outcome-driven misuse of Bradford Hill employed by Plaintiffs' experts.

IV. Plaintiffs' Briefs Are Rife With Other Misrepresentations.

Plaintiffs lace their briefs with a broad array of factual misstatements. Dismantling these misrepresentations reveals Plaintiffs' briefing for what it is: not a true *Daubert* challenge, but an improper attempt to impugn the credibility of Bayer's experts by distorting the facts.

A. Plaintiffs Misstate Basic Statistical and Epidemiological Concepts.

Where the primary evidence relied upon by Plaintiffs' experts is an epidemiological case-control study — here, Valenzuela — any arguments about general causation must be grounded in

[9] In fact, a new study presented this month at the annual meeting of the North American Neuro-Ophthalmology Society has found precisely the opposite: that "[u]se of a levonorgestrel IUD is ***not*** associated with an increased risk of IIH after adjusting for important potential confounders associated with both IUD use and IIH risk." Ex. F (attached hereto), DeLott L, Moniz M, Narayanaswamy P, Musch D, Cornblath W. *Idiopathic Intracranial Hypertension is not associated with levonorgestrel intrauterine device use.* NANOS Poster 2018 (emphasis added). Unlike the Valenzuela analysis, this study controlled for key confounders, such as obesity.

a solid basis of statistical argument. Yet misstatements of basic statistical principles, unsupported by any expert, pervade Plaintiffs' briefs. Key examples include:

Confounding: Plaintiffs use an inapt poker analogy to argue that Valenzuela's failure to control for IIH's greatest risk factor — obesity — is irrelevant, because IIH is a rare disease. *See, e.g.*, Pl. Omnibus Br. at 17-18; Pl. Barnhart Br. at 8-9; Pl. Langer Br. at 11. Plaintiffs' argument confuses the concepts of relative risk and absolute risk. While it is true that IIH is uncommon even in obese women of reproductive age, that speaks to the *absolute* risk of developing IIH. But the Valenzuela study reports an odds ratio, which is a measure of *relative* risk, and that is where the confounding comes in — because it remains the case that any obese woman of reproductive age has more than twenty times the risk of developing IIH relative to a non-obese woman of reproductive age. Ex. 22, Daniels 2007, at 637 fig. 1. As Dr. Barnhart explained, because Valenzuela is a case-control study,

> . . . you're starting with people that have a disease, so now the incidence doesn't matter. And if you picked everyone with the disease that was obese and you compared it to everybody that was thin, you are now comparing apples and oranges and the answer you'll get is simply garbage. It's wrong. So unless you can control for the factors, like more women are getting pseudotumor cerebri that are obese and more women are using Mirena because they're obese, you can't say that it's not the obesity that's the association and not the Mirena. . . . If you didn't control for obesity, you're going to be misled, get a wrong answer, and that's Epidemiology 101.

Pl. Barnhart Ex. B, Dep. at 43:20-44:16. The relative effects of confounding are not changed by the fact that the absolute numbers are small, and Plaintiffs have no expert sponsor for this misguided argument.

Statistical Significance and P-Values: In assessing whether the evidence supports an increased risk of IIH with Mirena use, Bayer's experts considered several studies examining rates of oral contraceptive use among women with IIH compared to women without IIH. These

data yield an especially crucial analysis, because oral contraceptive users are exposed to significantly higher levels of levonorgestrel or other progestins than Mirena users. Pl. Barnhart Ex. A, Rpt. at 85-87, Exhibits 1-2. The studies uniformly failed to show any statistically significant increase in oral contraceptive use among patients with IIH as compared to patients without IIH. *See* Ex. 23, Digre 1984; Ex. 25, Durcan 1988; Ex. 37, Ireland 1990; Ex. 33, Giuseffi 1991; Ex. 51, Radhakrishnan 1993; Ex. 39, Kilgore 2017. Given that oral contraceptive users are exposed to markedly higher levels of LNG than Mirena users, these data are consistent with the Bayer experts' finding that the available data do not support an increased risk of IIH with Mirena.

Plaintiffs' own experts have agreed that there is no evidence of increased IIH risk with oral contraceptive use. Ex. 4, Fraunfelder Dep. 16:7-14 (agreeing that "an association between oral contraceptives and IIH has been largely disproven"); Ex. 2, Darney Dep. 43:2-14 ("My opinion is that [oral contraceptives] do not [cause IIH]"). Undeterred by their own experts' testimony, Plaintiffs claim that the studies should not be considered because "none of the analyses came close to statistical significance." Pl. Omnibus Br. at 16; Pl. Langer Br. at 8. Plaintiffs' claim relies on a fundamental misinterpretation of the "P-values" in statistics. By convention, P-values are one tool used to assess whether a study found a statistically significant ***difference*** between two measures, and a P-value of less than 0.05 generally indicates a "significant" difference between the study arms. A P-value of 0.05 or greater means the study found no significant difference between the arms, confirming the null hypothesis: no measurable difference between "A" and "B." *See* Pl. Langer Ex. B, Dep. at 49:2-23; Pl. Barnhart Ex. B, Dep. at 17:12-18:10.

Plaintiffs' brief responds with a fiction: that a P-value of greater than 0.05 means the

study's results are not reliable at all. But this fundamentally flawed interpretation of statistics — nowhere endorsed by their experts — would render any study that failed to show a statistically significant difference unreliable and meaningless. This construction of significance makes no sense, and misinterpretations of statistical principles cannot support a *Daubert* challenge.

Case-Control Study Design and Interpretation: Using lawyer-generated equations, Plaintiffs claim that Dr. Langer's analysis of the Utah data in the Valenzuela study "produced control groups with rates of IIH higher than any population ever studied." Pl. Langer Br. at 16-18. Not only does this misportray Dr. Langer's analysis, but the assertion makes no sense: by definition, no one in the control group in a case-control study has the disease. Not surprisingly, Dr. Langer responded to Plaintiffs' counsel with "where do you get that" and "I can't speak for that" and pointed out that what he had shown was that there had been a "gross underestimate" of *Mirena usage* in the Utah controls. Pl. Langer Ex. A, Rpt. at 27; Pl. Langer Ex. B, Dep. 223:17-22. Plaintiffs do not offer any colorable attack on Dr. Langer's methodology by concocting an argument about "IIH rates" in a control group which by definition *cannot have IIH*.

The meaning of "controlled studies": Plaintiffs also attack Dr. Dalton's statement that "the previously hypothesized relationship between sex hormones and IIH has been disproven by controlled studies," Pl. Dalton Ex. D, Rpt. 32-33, claiming that "there are no 'controlled studies'" because such studies would have "the objective of causing [IIH]" and "would be blatantly unethical." Pl. Omnibus Br. at 24. But a controlled study such as a clinical trial *can* examine adverse effects (such as nausea, or here, IIH) without intentionally inflicting those side effects on patients; this is the fundamental nature of capturing all adverse events in clinical trials and does not mean the trial is being conducted to measure harm. Second, an observational epidemiology study such as a case-control study can control for known risk factors when

assessing whether there is any increased risk of a given outcome (here, IIH) among medication users. Here, controlled studies such as oral contraceptive studies have not demonstrated any increased rate of oral contraceptive use among IIH patients as compared to non-IIH patients. Those controlled oral contraceptives studies, along with the Etminan cohort study, are the very "controlled studies" that Dr. Dalton discussed in her report. Pl. Dalton Ex. D, Rpt. 19. Plaintiffs' misreading of Dr. Dalton's testimony does not support a *Daubert* challenge.

In short, where statistics are concerned, Plaintiffs' briefs are filled with irreparably mistaken arguments untethered from the opinions of their own experts and from basic epidemiologic principles. Misstatements about statistical matters cannot support the exclusion of Bayer's experts.

B. Plaintiffs Misrepresent Readily Provable Facts.

The misrepresentations in Plaintiffs' briefs are not a matter of judgment, where two reasonable parties could disagree on the interpretation of unclear data. Instead, Plaintiffs make numerous demonstrably false claims. For example:

Misrepresentation of FDA's position on using adverse event data: Plaintiffs argue that "Dr. Barnhart's opinion is cursory, subjective, and made without reference to any literature supporting their methods," because he and Bayer "absurdly compar[e] the rate at which adverse events are reported to the rate of the disease in the population, *a method explicitly rejected by the FDA*[.]" Pl. Barnhart Br. at 15 (emphasis added). In fact, FDA urges the exact *opposite* of what Plaintiffs' claim and explicitly recommends "comparisons of incidence rates or reporting rates to background rate estimates[.]" Ex. 78, 2005 Guidance at 10-11.

Misrepresentation of experts' use of oral contraceptive data: Plaintiffs claim that Bayer's experts "never explain how they can use aggregated 'oral contraceptives' to draw conclusions about oral contraceptives containing levonorgestrel" and that "also included

synthetic forms of estrogen." Pl. Omnibus Br. at 15. This accusation is false. As discussed in greater detail in oppositions to the motions to exclude individual experts, Bayer's experts directly addressed both of these matters. First, Bayer's experts cite literature showing that LNG/norgestrel (two formulations of the same active drug) were predominant progestins used in combined oral contraceptives in the 1980s and early 1990s, when the oral contraceptive IIH studies were conducted. *See, e.g.*, Pl. Hewitt Ex. A, Rpt. 19-20; Pl. Hewitt Ex. D, Dep. 234:24-235:5; Pl. Langer Ex. A, Rpt. at 19-20; Pl. Lee Ex. A, Rpt. at 22-23. Second, Bayer's experts address Plaintiffs' theory regarding estrogen and SHBG binding, including by directly addressing plaintiff expert Dr. Plunkett's theory about relative binding and free LNG. *See, e.g.*, Pl. Langer Ex. A, Rpt. at 19-20; Pl. Hewitt Ex. A, Rpt. at 24-25; Pl. Lee Ex. A, Rpt. at 22-23.

Misrepresentation as to whether oral contraceptive studies controlled for confounding: Plaintiffs wrongly claim that no oral contraceptive study "controlled for confounding at all." Pl. Omnibus Br. at 15-16. In fact, several of the studies they cite explicitly did control for weight, the major risk factor for IIH. *See, e.g.*, Ex. 33, Giuseffi 1991 ("For differences of weight and of recent weight gain between patients and controls, we used a two-tailed independent T test."); Ex. 51, Radhakrishnan 1993 ("We assessed the predictive power of the following variables utilizing a multiple logistic regression model. . . body weight."); Ex. 39, Kilgore 2017 ("With multivariate analysis including BMI, the OR was 0.67 (95% CI, 0.26-1.76; P-value = 0.415)").

Misrepresentation of Dr. Lee's review of materials: Plaintiffs offer no support for their assertion that "nothing in Dr. Lee's report shows him doing anything other than reviewing Bayer's signal assessments and then performing the exact same analysis Bayer performed[,]" and that Dr. Lee "admits he reviewed virtually nothing." Pl. Lee Br. at 1, 2. These accusations are demonstrably false. In preparing his 56-page report, Dr. Lee drew from his review of more than

100 pieces of literature and dozens of other documents. Pl. Lee Ex. A, Rpt. Materials List.

Misrepresentation of Dr. Barnhart's review of materials: Plaintiffs hurl a baseless accusation that Dr. Barnhart "did not even bother to mention which of those three [plaintiffs' mechanism-related] experts he was discussing" and "made no effort to grapple with any of the relevant literature addressing the pathophysiology of [I]IH or the biological effects of levonorgestrel." Pl. Barnhart Br. at 20. In fact, Dr. Barnhart states explicitly in his report: "I also address certain points regarding the mechanisms proposed by Drs. Darney, Johanson, Plunkett, and Salpietro." Pl. Barnhart Ex. A, Rpt. 62. A simple review of Dr. Barnhart's list of Materials Considered demonstrates that he reviewed dozens of articles cited by Plaintiffs to support their mechanism theories and cited several articles in response; his report devotes several pages to debunking plaintiffs' mechanism theories.

C. Plaintiffs Misrepresent Bayer's Experts' Testimony.

In both their omnibus brief and in their individual briefs, Plaintiffs misrepresent the experts' testimony on numerous issues. Prime examples include:

Misrepresentation of experts' use of Etminan cohort study: Plaintiffs accuse Bayer's experts of relying on the Etminan cohort study "as critical support for their overall conclusions" without addressing "any of Dr. Friedman's criticism[s] or any other limitations[.]" Pl. Omnibus Br. at 10-12. This is untrue. Bayer's experts noted key limitations of the Etminan cohort study; many of them noted Dr. Friedman's particular criticisms; and none of them relied on the Etminan cohort study as "critical support" for their conclusions, instead treating it as a flawed piece of evidence that nonetheless failed to offer any support for Plaintiffs' causation theory.[10]

[10] *See, e.g.*, Pl. Cestari Ex. A, Rpt. at 15-16; Pl. Gossett Ex. A, Rpt. at 17-18; Pl. Hewitt Ex. A, Rpt. at 23; Pl. Van Stavern Ex. B, Rpt. at 9-10; Pl. Rizzo Ex. B, Rpt. at 10-11; Pl. Barnhart Ex.

Conspicuously, the only Bayer expert Plaintiffs name in this portion of their Omnibus Brief is Dr. Newman — presumably their strongest example — but Dr. Newman's expert report expressly states that "[b]oth of [Etminan's] analyses suffer from a number of flaws" and then enumerates those flaws. Pl. Newman Ex. K, Rpt. at 8-9. Indeed, among the flaws identified by Dr. Newman are the very flaws discussed by Dr. Friedman in her Letter to the Editor. *Compare, e.g.*, Ex. G (attached hereto), Friedman 2016 ("Search terms for this analysis were even more egregious than in the first methodology, including obstructive hydrocephalus as well as cerebral edema, conditions which are unrelated to using hormonal contraceptives and distinct entities from PTCS."), *with* Pl. Newman Ex. K, Rpt. at 8-9 ("use of search terms that were far too broad . . . [and] inclusion of terms that would actually preclude a diagnosis of IIH, such as cerebral edema, obstructive hydrocephalus, and normal pressure hydrocephalus").

Misrepresentation of experts' positions on LNG serum level: Plaintiffs falsely claim that Bayer's experts give opinions about LNG serum levels that contradict the Mirena label. Pl. Omnibus Br. at 20-21. Plaintiffs' argument boils down to semantic nitpicking about the difference (if any) between a "few weeks" and a "few months." As Plaintiffs note, Bayer's experts generally state that LNG serum levels are highest in the "first few months" and then decline thereafter. Pl. Omnibus Br. at 21 n.30. The published Apter analysis of the various doses of LNG-IUSs supports their testimony: Apter found that LNG serum levels were highest within the first few weeks and months, dropped dramatically by the one-year mark, and gradually declined thereafter. Ex. H (attached hereto), Apter 2014 at Fig. 1A; *see also* 7.e2, Supp. Table 2. The Mirena label is not to the contrary. It states that a "stable serum

---

A, Rpt. at 33-35; Pl. Dinkin Ex. 4, Rpt. at 8-9; Pl. Newman Ex. K, Rpt. at 8-9; Pl. Langer Ex. A, Rpt. at 23-24; Pl. Lee Ex. A, Rpt. at 29-30; Pl. Dalton Ex. D, Rpt. at 19.

concentration . . . occurs after the first few weeks following insertion of Mirena." Ex. 68, Mirena Label. Picking up at the one-year mark, the label then states that LNG serum levels at 12 and 24 months were 180±66 pg/mL and 192±140 pg/mL, and further states that LNG serum levels declined to 159±59 pg/mL after 60 months. *Id.* This description is entirely consistent with the Apter study and with Bayer's experts' testimony.

Misrepresentation of experts' use of Valenzuela: Plaintiffs flood their individual *Daubert* papers with other mischaracterizations of how Bayer's experts evaluated Valenzuela. In one egregious example, Plaintiffs claim that Dr. Van Stavern "has agreed that there is no control study that supports his opinion." Pl. Van Stavern Br. at 4. In fact, in his 2018 report, Dr. Van Stavern expressly states the opposite: that the Valenzuela case-control study "supports the conclusion that there is no causal association." Pl. Van Stavern Ex. B, Rpt. at 12. Yet Plaintiffs ignore Dr. Van Stavern's 2018 report and cite instead to his deposition testimony from 2016 — before the Valenzuela study was published in 2017 — in which Dr. Van Stavern answered truthfully that no case-control study existed *at that time*. Pl. Van Stavern Ex. D, 5/17/16 Dep. at 68:25-69:6.

***Misrepresentation of Dr. Barnhart's explanation of his methodology*:** Contrary to Plaintiffs' claim, Dr. Barnhart did not testify that he "applied subjective methods when assessing literature, adjusting his analysis to suit his conclusions." Pl. Barnhart Br. at 4. In fact, Dr. Barnhart explicitly testified that he uses a consistent methodology to analyze the literature, regardless of its findings: "[y]ou don't apply different methodology. You don't apply different weights of the evidence. . . . So you want to be sure that a positive association is true. Of course, you want to be sure [a] negative association is true, too. . . ." Pl. Barnhart Ex. B, Dep. 117:18-118:18.

Misrepresentation of Dr. Barnhart's testimony about his ability to conduct an IIH differential diagnosis: In a stark example of misrepresenting an expert's testimony, Plaintiffs claim that "Dr. Barnhart admitted he would not be qualified to perform a differential diagnosis of IH[.]" Pl. Barnhart Br. at 20. Although Plaintiffs provide a block quotation supposedly supportive of this point, they use ellipses to omit Dr. Barnhart's direct answer to the question of whether he could conduct a differential diagnosis on a patient with IIH: "So a differential diagnosis, of course." Pl. Barnhart Ex. B, Dep. 127:10-17.

V. Plaintiffs Make Lawyer-Crafted Arguments With No Experts to Sponsor Them.

In both their omnibus brief and individual briefs, Plaintiffs frequently premise their arguments on unreliable statistical and scientific conjecture, unsupported by any of their own expert witnesses:

Controlling for obesity in Valenzuela: Plaintiffs' Footnote 26 presents counsels' own adjustment to account for obesity in Valenzuela's findings, and counsels' own claim that IIH patients still have increased odds of using Mirena after such an adjustment. Pl. Omnibus Br. at 18 n.26. None of Plaintiffs' experts did any such calculation.

Estimating the percentage of reproductive-age women in Utah who are at risk for unintended pregnancy: When estimating what percentage of reproductive-aged women in Utah use Mirena — a relevant calculation, given that Valenzuela admitted they failed to adequately estimate this figure in their control population — one element of the calculation requires estimating the percentage of women in this age range who are "at risk for unintended pregnancy." Bayer's experts turn to peer-reviewed, published data from sources such as CDC for this estimate. *See, e.g.*, Pl. Barnhart Ex. A, Rpt. and Reliance List; Pl. Langer Ex. A, Rpt. and Reliance List; Pl. Lee Ex. A, Rpt. and Reliance List. Plaintiffs dismiss this approach in favor of their lawyer-initiated estimation of the percentage of Utah women at risk for unintended

pregnancy. Again without input or sponsorship from their actual experts, the lawyers cobble together pieces of Census data, "weighted" and "unweighted" data from a study (where those terms were *not defined by the study*), and unsubstantiated assumptions about population growth rates. Pl. Barnhart Br. 11-13.

Misinterpreting oral contraceptive studies: Plaintiffs suggest that the oral contraceptive data, if anything, find "an increased use of oral contraceptives among patients with [I]IH." Pl. Omnibus Br. at 16 n.24. But Plaintiffs' own experts have testified that the oral contraceptive data does *not* demonstrate any relationship with IIH. Ex. 4, Fraunfelder Dep. 16:7-14 (agreeing that "an association between oral contraceptives and IIH has been largely disproven"); Ex. 2, Darney Dep. 43:2-14 ("My opinion is that [oral contraceptives] do not [cause IIH]").

Identifying supposed methodological limitations in data: Plaintiffs argue that seven of the articles that Dr. Rizzo relies upon have "substantial limitations in both their methodology and their application to Dr. Rizzo's exercise." Pl. Rizzo Br. at 8-9. But none of these articles are discussed by the plaintiff experts or even listed on their reliance lists.

Plaintiffs' unsupported, erroneous lawyer argument on scientific topics simultaneously highlights the unreliability of their own assertions and the lack of any basis to exclude Bayer's experts' testimony.

CONCLUSION

For the foregoing reasons, and for the additional reasons set forth in Bayer's individual opposition briefs, Bayer respectfully requests that the Court deny Plaintiffs' *Daubert* motions to exclude the testimony of Bayer's experts.

Dated: March 15, 2018

Respectfully submitted,

s/ Paul W. Schmidt

Paul W. Schmidt
Michael X. Imbroscio
Covington & Burling LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
Telephone: (202) 662-5272
Facsimile: (202) 778-5272
pschmidt@cov.com
mimbroscio@cov.com

Shayna S. Cook
Goldman Ismail Tomaselli Brennan & Baum LLP
564 West Randolph Street, Suite 400
Chicago, Illinois 60661
Telephone: (312) 681-6000
Facsimile: (312) 881-5191
scook@goldmanismail.com

James Shepherd
Shook Hardy & Bacon LLP
600 Travis Street, Suite 3400
Houston, TX 77002
Telephone: (713) 227-8008
Facsimile: (713) 227-9508
eshepherd@shb.com

Attorneys for Defendants Bayer HealthCare Pharmaceuticals Inc., Bayer Pharma AG, and Bayer Oy

CERTIFICATE OF SERVICE

I hereby certify that on this 15th day of March, 2018, a copy of the foregoing has been served on the interested parties in this action via ECF:

Martin D. Crump
Davis & Crump PC
2601 Fourteenth Street
Gulfport, Mississippi 39501
martincrump@daviscrump.com
Co-Lead Counsel for Plaintiffs

Lawrence L. Jones II
Jones Ward PLC
The Pointe
1205 East Washington Street, Suite 111
Louisville, Kentucky 40206
larry@jonesward.com
Co-Lead Counsel for Plaintiffs

Maxwell S. Kennerly
Kennerly Loutey, LLC
PO Box 30049
Elkins Park, Pennsylvania 19027
msk@thlawyer.com
Liaison Counsel for Plaintiffs

/s/ Paul W. Schmidt
Paul W. Schmidt